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Review Article

Molnupiravir and Combination of Nirmatrelvir and Ritonavir (Paxlovid™) - Oral Anti-viral Drugs in COVID-19: A Systematic Review

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A B S T R A C T

The COVID-19 pandemic situation demands the discovery of newer drugs and/ or repurposing of the existing drugs. The anti-viral drugs approved for COVID-19 are remdesivir and favipiravir. Two more directly acting oral anti-viral drugs have been granted Emergency Use Authorization by US-FDA, molnupiravir on December 23, 2021, and nirmatrelvir and ritonavir (Paxlovid™) on December 22, 2021. Molnupiravir, an RNA-dependent RNA polymerase (RdRp) inhibitor, has also been approved in the UK and is under review with other regulatory agencies. Paxlovid™ (a combination of the new anti-viral drugs nirmatrelvir and ritonavir) has been developed and approved by US-FDA and CDSCO, India. Nirmatrelvir acts by inhibiting 3CL (chymotrypsin-like) protease enzyme and it is combined with ritonavir to slow down its breakdown by cytochrome P450 enzymes and to increase the bioavailability. Both molnupiravir and Paxlovid™ have been approved for mild and moderate COVID-19 and in patients who have a higher risk of disease progression to severe disease including hospitalisation and death. This article systematically reviews the clinical trials of molnupiravir and Paxlovid™ that evaluated their efficacy and safety against COVID-19 in both published and unpublished literature.

Keywords: COVID-19, Molnupiravir, Paxlovid™, Nirmatrelvir, Ritonavir, Systematic Review

Introduction

Since the onset of COVID-19 in December 2019, pharmaceutical companies have been trying to find out potential drugs that could act against SARS-CoV-2 (Severe Acute Respiratory Syndrome Coronavirus-2). The directly acting anti-viral drugs that are approved for COVID-19 are remdesivir and favipiravir. In addition, US-FDA (United States Food and Drug Administration) approved two other anti-viral drugs, molnupiravir and Paxlovid™.[1,2] Remdesivir is approved for treating hospitalised COVID-19 patients and favipiravir for mild to moderate COVID-19. Even people who are vaccinated with the COVID vaccine can also get asymptomatic or mild to moderate infection with SARS-CoV-2. Hence, there is a constant need for new drugs or repurposing of the existing drugs for treating asymptomatic and mild to moderate or severe COVID-19.

Molnupiravir is an oral anti-viral drug, developed by Merck and Ridgeback Biotherapeutics that has shown promising results in its phase II and phase III trials and has been approved for use in the UK. US-FDA gave Emergency Use Authorisation (EUA) for molnupiravir on December 23, 2021, to be used in patients more than 18 years of age for treating mild to moderate COVID-19 and in patients with high risk for progression to severe disease including hospitalisation and death. The dosage recommendation for molnupiravir is 800 mg, to be taken 12th hourly for 5 days.[1]

A combination of a new anti-viral drug, nirmatrelvir, and low-dose ritonavir, developed by Pfizer Pharmaceuticals under the brand Paxlovid™, has also been granted EUA by US-FDA on December 22, 2021,[2] and in India by CDSCO in April 2022. It has been approved for treating mild to moderate COVID-19 patients aged more than 12 years, weighing a minimum of 40 kilograms and in those with a high risk of disease progression to severe COVID-19, including hospitalisation and death.

Molnupiravir

Molnupiravir has good antiviral activity against many viruses like influenza, corona (including SARS-CoV-2), and encephalitic viruses in non-clinical studies. It was developed as a prodrug, as the active form, EIDD-1931 showed poor bioavailability in preclinical studies. The drug was originally developed for influenza by Emory University (USA), and it was in the stage of preclinical testing during the onset of the COVID-19 pandemic. Later, the clinical development of molnupiravir shifted towards the management of COVID-19.[3]

Mechanism of Action

Molnupiravir inhibits the viral RNA-dependent RNA polymerase (RdRp) similar to favipiravir and remdesivir. It is a prodrug and gets converted to an active molecule i.e., EIDD-1931 in the body, which then undergoes phosphorylation by the host kinases to EIDD-1931 triphosphate. This acts as a competitive substrate for RdRp, resulting in mutated copies of RNA, thereby inhibiting the normal function of RdRp, which is crucial for viral replication.[3]

Preclinical Studies

Molnupiravir showed potent anti-viral activity against the influenza viruses in rodents and non-human primates. Further, it demonstrated a therapeutic window (antiviral efficacy vs cytotoxicity) of > 1713 in the preclinical studies. The efficacy has also been demonstrated not only against SARS-CoV but also against MERS-CoV (Middle East Respiratory Syndrome Corona Virus) including remdesivir-resistant viruses when given orally.[4,5]

In the animal model (ferrets) of SARS-CoV-2, molnupiravir, when given orally, reduced the viral load significantly in the respiratory tract and also prevented the transmission of the virus to untreated contact animals.[6]

Regulatory Approval Status

Molnupiravir has been approved by the regulatory agency of the United Kingdom (UK)- "Medicines and Healthcare Products Regulatory Agency (MHRA)" on November 4, 2021, for COVID-19. The UK was the first country to give regulatory approval for molnupiravir,[7] followed by US-FDA on December 23, 2021. Later, the new drug applications for marketing authorisation of this drug have been submitted to other drug regulatory agencies including"Central Drugs Standard Control Organization (CDSCO, India)" and "European Medicines Agency (EMA)".[8]

Paxlovid™

Paxlovid™ is the combination of two drugs nirmatrelvir 300 mg and an anti-retroviral drug ritonavir (100 mg). Lufotrelvir, a 3-chymotrypsin-like protease inhibitor was developed by Pfizer for COVID-19 which was not active orally. It has to be given through an intravenous route in the hospital setting. Lufotrelvir was chemically modified to develop an orally active anti-COVID drug PF-07321332 (nirmatrelvir).[9] It is combined with ritonavir to slow down the breakdown of nirmatrelvir by cytochrome P_{450} enzymes and to increase its bioavailability.

Pfizer designed the oral drug, nirmatrelvir, by incorporating a few structural alterations in lufotrelvir. Lufotrelvir has been evaluated for its efficacy against COVID-19 in hospitalised patients while PF-07321332 in patients with mild to moderate disease, who did not require hospitalisation. Pfizer pharmaceuticals, in their press release on November 5, 2021, stated that after positive results from the phase 1 studies of lufotrelvir and PF-07321332, they started the phase 2/3 trials but the reports of phase 1 trials for both the protease inhibitors were not available in the public domain.

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Preclinical Trials

There is no significant data available on the preclinical studies of nirmatrelvir. The data available is with regard to another molecule (PF-00835231), an active component of the prodrug lufotrelvir. In the mice model of SARS-CoV-2, PF-00835231was found to exhibit significant antiviral activity as evidenced by the reduction in the viral titres in the lung of infected animals after dosing with 100 mg/kg twice daily as a subcutaneous injection.[10]

Mechanism of Action

3CLpro (3-chymotrypsin-like protease) is the vital enzyme that is responsible for generating various non-structural proteins in the COVID virus including helicase, RdRp and 3CLpro itself. Unlike the other anti-viral drugs available for COVID-19 such as remdesivir, favipiravir, and molnupiravir, which act by inhibiting RNA-dependent RNA polymerase, PF-07321332 acts by inhibiting 3CL protease (3-chymotrypsin like protease), the vital enzyme responsible for the multiplication of SARS-CoV-2 virus.[11]

Development

The 3CL protease inhibitor, PF-00835231, developed 15 years back for SARS-CoV-1 was found to have activity towards the SARS-CoV-2 virus in-vitro. Later, the prodrug of PF-00835231, lufotrelvir (PF-07304814), was evaluated for its efficacy in preclinical models and in hospitalised COVID-19 patients. But, lufotrelvir should be administered as an IV infusion, like remdesivir due to poor oral bioavailability. In order to overcome this limitation, scientists modified it chemically to develop the orally active nirmatrelvir for patients with mild to moderate disease.[11]

This article systematically reviews the clinical trials evaluating the efficacy and safety of molnupiravir and Paxlovid™ against COVID-19, available in the public domain.

Materials and Methods

The following types of studies with the results, available in the public domain for molnupiravir and Paxlovid™ were included in this systematic review:

- Phase 1 clinical trials
- Phase 2 clinical trials
- Phase 3 clinical trials

PubMed, Google Scholar, EMBASE, Web of Science and SCOPUS were searched for published data. The authors also searched the preprint servers like medRxiv, SSRN preprint, and bioRxiv and the clinical trial registries like clinicaltrials.gov and CTRI (Clinical Trials Registry, India) for getting information about the unpublished data.

The keywords used for the search were molnupiravir, EIDD-1931, Paxlovid, Pfizer, Merck, COVID-19, oral drugs, and SARS-CoV-2.

Results

Molnupiravir

A total of 3 trials (that include phases 1, 2, and 3 trials) were found for molnupiravir. Among them, the results of the phase 1 trial were published in a peer-reviewed journal while the phase 2 trial data was in the preprint server and had not yet been peer-reviewed. The data of interim analysis of the phase 3 trial was presented in the press release given by Merck and it could not be seen in preprint or any peer-reviewed literature.[12]

Phase I

The analyses of the phase 1 study, which evaluated the safety, tolerability and pharmacokinetics (PK) of molnupiravir, have been published in Antimicrobial Agents and Chemotherapy Journal in 2021.[13] The phase 1 trial was carried out among 130 healthy volunteers. The subjects were randomly assigned to receive either molnupiravir or a placebo in a 3:1 ratio. In the single ascending dose study, a single dose of molnupiravir (50 to 1600 mg) was administered and in the multiple ascending dose study, the subjects received molnupiravir (50 to 800 mg) or placebo twice daily. In both single and multiple ascending dose studies, the treatment was given for 5.5 days. The follow-up of the subjects was done for 14 days after dosing. The PK profile was evaluated in the fasting and fed state with 200 mg of molnupiravir. The absorption rate was similar in the fasting and fed states on prolonged exposure.[13]

The study showed that molnupiravir had good absorption at concentrations of 50 to 1600 mg in a dose-dependent manner. The plasma half-life was dependent on dose and ranged between 0.9 and 7.08 hours. The most common adverse event observed was headache and the drug did not show any adverse impact on the vital functions, haematological parameters, and ECG. Hence, molnupiravir was considered safe at doses between 50 and 1600 mg. The effective dose was reported to be 200 to 800 mg.[13]

Phase 2

The results of the phase 2a trial of molnupiravir were published in medRxiv preprint.[8] The study participants included outpatients who had laboratory-confirmed COVID-19 infection within 96 hours and presented with COVID-19 symptoms within a week (7 days) of initiation of treatment. Subjects were randomised into 4 groups - 200 mg, 400 mg, and 800 mg molnupiravir, and placebo. The drugs were given 12th hourly orally for 5 days.

The primary outcome was the "time taken for viral RNA clearance (using RT-PCR of nasopharyngeal swabs) and the secondary efficacy outcome measures included time for elimination of infectious virus (assay performed with Vero C1008 cells) from the nasopharyngeal sample and median

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change in the viral RNA from baseline to days 3, 5 and 7".

The safety outcomes included adverse events of grade 3 and above and the adverse events that led to treatment discontinuation. In addition, the clinical outcomes (duration and severity of self-reported COVID-19 symptoms) and immunological outcomes (antibody levels) were assessed in this trial.[8]

The median duration for viral RNA clearance in the nasopharyngeal samples was 14 days with 800 mg molnupiravir while it was 27 days with placebo (p = 0.001). The percentage of subjects who became negative for SARS-CoV-2 at the end of the study (28 days) was 92.5% with 800 mg molnupiravir, while it was 91.3% and 78.7% with 400 and 200 mg respectively. In the placebo group, 80.3% of the subjects achieved viral negativity.[8]

On day 3, 16.7% of subjects who received a placebo had the infectious virus in their nasopharyngeal samples as against 1.9% who received 800 mg molnupiravir (p = 0.02). On day 5, none of the participants had the infectious virus in the molnupiravir group (400 or 800 mg) whereas, 11.1% in the placebo group had the virus in the nasopharyngeal sample (p = 0.03). The proportion of subjects who had infectious virus isolated was significantly less with molnupiravir (400/ 800 mg) as compared to 200 mg molnupiravir or placebo, thus demonstrating a clear dose-dependent response.[8]

The decrease in viral load was significantly high with 800 mg molnupiravir compared to the other 3 groups. The proportions of subjects with positive antibody (IgA, IgG, and IgM) to SARS-CoV-2 at baseline were 15%, 30%, 35.3%, and 18.2% in molnupiravir 200, 400, and 800 mg, and placebo groups respectively at baseline. At the end of the study, 99.2% of subjects in the molnupiravir group developed antibodies to the virus compared to 96.5% of subjects who were treated with a placebo.[8]

The adverse events that led to treatment discontinuation occurred in 1.4% of subjects in the molnupiravir group compared to 1.6% in the placebo group. Adverse events of grade 3 and above were seen in 8.1% and 5% of the participants in the placebo group and molnupiravir respectively. Adverse events that resulted in hospitalisation were seen in 1.6% of subjects in the placebo group, 3.2% with 400 mg molnupiravir and 1.8% with 800 mg molnupiravir. 1 subject died in the placebo group after the completion of the study i.e., 28 days. The clinical symptoms' duration and severity did not show significant differences among the groups over 28 days.[8]

Phase 3

The results of the phase 3 trial of molnupiravir have not been published in the literature. Merck has given a press release on October 1, 2021, where the details of the interim analysis of the phase 3 trial were shared. The data of 775 subjects who were enrolled in the phase 3 trial were evaluated in the interim analysis to assess the efficacy of molnupiravir in at-risk (patients should have at least 1 risk factor associated with poor disease outcome at the time of enrollment), non-hospitalised, mild to moderate COVID-19 patients. The primary endpoint for efficacy assessment was the "percentage of subjects who end up in hospitalisation and/ or death from the time of randomisation to day 29".[12]

Hospitalisation and/ or death were seen in 7.3% of the subjects (28 out of 285) who received molnupiravir while it was 14.1% (53 out of 377 subjects) with placebo (p = 0.0012). 8 subjects in the placebo group died through day 29, whereas no deaths were reported in the molnupiravir group. Thus, the results of the interim analysis showed that molnupiravir significantly lowered hospitalisation and/ or death in mild to moderate COVID-19 cases.[12]

Current Trials of Molnupiravir in India

Twelve (12) multicentric trials have been registered in the Clinical Trials Registry, India (CTRI) and are currently ongoing in India to evaluate the efficacy of molnupiravir in COVID-19.[14]

Paxlovid™

In the press release, Pfizer shared the report of the interim analysis of phase 2/ 3 study of the investigational drug (Paxlovid™ – a combination of PF-07321332 and low dose ritonavir) in non-hospitalised COVID-19 patients who had the risk of disease progression. The acronym of the trial is "EPIC-HR (Evaluation of Protease Inhibition for COVID-19 in High-Risk Patients)".[15]

Patients with laboratory-confirmed COVID-19 presenting with mild to moderate symptoms within 5 days and with at least one underlying comorbidity associated with the risk of progression to severe COVID, were included in the study. The subjects were randomised in a 1:1 ratio to receive either Paxlovid™ or placebo, 12th hourly for 5 days.[15]

The primary efficacy outcome measure was the "proportion of participants with hospitalisation related to COVID-19 or death from any cause from baseline through the end of the study (day 28)". The interim analysis showed that Paxlovid™ reduced the risk of COVID-19-related hospitalisation or death due to any cause to 89% within 3 days of the onset of symptoms. Three out of 389 (0.8%) subjects in the Paxlovid™ group were hospitalised with no deaths through 28 days while in the placebo group significantly higher number of subjects, 27 out of 385 (7%) were hospitalised and 7 subjects among them subsequently died (p < 0.0001).[15]

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Table 1.Characteristics of the Clinical Trials of Molnupiravir and Paxlovid™

Study, Year	Phase of the Trial	Study Type	Type of Subjects	No. of Subjects	Intervention	Follow Up	Outcome(s)	Comments
Painter et al., 2021[13]	Phase 1	Randomised, crossover, open-label study in fasting and fed states	Healthy subjects	130	i) Single dose of molnupiravir (50-1600 mg) or placebo ii) Multiple dose of molnupiravir (50-800 mg) or placebo iii) Food effect 200 mg molnupiravir	14 days	Safety Tolerability Pharmacokinetic profile in fasting and fed state	A single dose of 50-1600 mg for 5.5 days was found to be safe and well tolerated. A significantly higher number of subjects in the placebo group had adverse events compared to molnupiravir in both single-dose (43.8% vs. 35.4%) and multiple-dose studies (50.0% vs. 42.9%).
Fischer et al., 2021[8]	Phase 2	Patients with SARS-CoV-2 infection (mild to moderate)		202	200, 400, and 800 mg of molnupiravir and placebo	28 days	Primary outcome Time taken for viral RNA clearance Secondary outcomes. Time to eliminate infectious virus (assay performed with Vero C1008 cells) from nasopharyngeal sample	The median time for viral RNA clearance in the nasopharyngeal samples was 14 days with 800 mg molnupiravir while it was 27 days with placebo (p = 0.001). The proportion of subjects who became negative for SARS-CoV-2 at the end of the study (28 days) was 92.5% with 800 mg molnupiravir, while it was 91.3% and 78.7% with 200 and 400 mg respectively. In the placebo group, 80.3% of the subjects achieved viral negativity. On day 3, 16.7% of subjects who received placebo had the infectious virus in their nasopharyngeal sample as against 1.9% who received 800 mg molnupiravir (p = 0.02). On day 5, none of the participants had the infectious virus in the molnupiravir group (400 or 800 mg) whereas, 11.1% of the subjects in the placebo group had the virus in the nasopharyngeal sample (p = 0.03).

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							Median change in the viral RNA from baseline to days 3, 5, and 7. Safety outcomes included adverse events of grade 3 and above and the adverse events that led to treatment discontinuation. Clinical outcomes (duration and severity of self-reported COVID-19 symptoms). Immunological outcomes	The proportion of subjects who had infectious virus isolated was significantly less with 400 and 800 mg of molnupiravir as compared to 200 mg or placebo, thus demonstrating a clear dose-dependent response. The reduction in viral load through days 3 to 28 was significantly high with 800 mg molnupiravir compared to the other 3 groups. The proportions of subjects with positive antibody (IgA, IgG and IgM) to SARS-CoV-2 at baseline were 15%, 30%, 35.3%, and 18.2% in molnupiravir 200, 400, and 800 mg and placebo groups respectively at baseline. At the end of the study, 99.2% of subjects treated with molnupiravir developed antibodies to the virus compared to 96.5% of subjects in the placebo group. The adverse events that led to treatment discontinuation occurred in 1.4% of subjects with molnupiravir compared to 1.6% with placebo. Adverse events of grade 3 and above were seen in 5% and 8.1% of the subjects in molnupiravir and placebo groups respectively. Adverse events that resulted in hospitalisation were seen in 1.6% in the placebo group, 3.2% with 400 mg molnupiravir and 1.8% with 800 mg molnupiravir. 1 subject died in the placebo group after the completion of the study i.e., 28 days. The clinical symptoms' duration and severity did not show significant differences among the groups over 28 days.

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Press release by Merck, 2021[12]	Phase 3	Multicentric, randomised, double-blinded, placebo-controlled	Patients with SARS-CoV-2 infection (mild to moderate)	775	Molnupiravir and placebo	29 days	Hospitalisation and/ or death	Hospitalisation and/ or death were seen in 7.3% of the subjects who received molnupiravir while it was 14.1% in the placebo group ($p = 0.0012$). 8 subjects in the placebo group died, whereas no mortality was seen in molnupiravir group.
Pfizer's press release, 2021[15]	Phase 2/3	Multicentric, randomised, double-blinded, placebo-controlled	Patients with SARS-CoV-2 infection (mild to moderate)	-	PaxlovidTM and placebo	28 days	Hospitalisation and/ or death	The interim analysis showed that PaxlovidTM reduced COVID-19-related hospitalisation or death due to any cause to 89% within 3 days of the onset of symptoms. 3 out of 389 (0.8%) subjects in the PaxlovidTM group were hospitalised with no deaths through 28 days while in the placebo group significantly higher number of subjects, 27 out of 385 (7%), were hospitalised and 7 subjects among them subsequently died ($p < 0.0001$). When subgroup analysis was done in patients who were given treatment within 5 days of symptom onset, a similar difference was noted between the groups: 1% (6 out of 607) of subjects were hospitalised in PaxlovidTM group and no death was reported. In the placebo group, 6.7% (41 out of 612) were hospitalised with mortality in 10 patients ($p < 0.0001$). Throughout the study period i.e., 28 days, there were no deaths reported with PaxlovidTM as against 10 deaths (1.6%) in the placebo group.

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Sub-group analysis was done for patients who were offered treatment within 5 days of onset of COVID-19 symptoms which showed a similar difference between the groups: 1% (6 out of 607) of subjects were hospitalised in the Paxlovid™ group, and no death was reported. In the placebo group, 6.7% (41 out of 612) were hospitalised with mortality in 10 patients ($p < 0.0001$). Throughout the study period i.e., 28 days, there were no deaths reported with Paxlovid™ as against 10 deaths (1.6%) in the placebo group.[15]

Approval Status

Paxlovid™ has been given EUA by US-FDA and approved by CDSCO in April 2022. The New Drug Application for the marketing of Paxlovid™ is under review with other regulatory agencies.

The characteristics of the clinical trials of molnupiravir and Paxlovid™ (with results) are summarised in Table 1.

Discussion

The two orally active anti-COVID drugs, molnupiravir and Paxlovid™ have been evaluated in non-hospitalised COVID-19 patients with mild to moderate disease, who had at least one comorbidity/ underlying condition that could lead to progression to severe COVID-19. The patients were followed up for 28 days from the start of treatment in the trials of both molnupiravir and Paxlovid™. The primary efficacy outcome was the same for the trials of both drugs, i.e., hospitalisation due to COVID-19 and/ or death due to any cause throughout the study period (from baseline through 28 days). The duration of treatment for both drugs is 5 days with the drugs given twice daily. The trial results, though publicly available in the press release of the pharmaceutical companies of both drugs have not been published in peer-reviewed literature.

The interim analysis report of the Phase 3 trial, released by Merck for molnupiravir stated that 7.3% of subjects in molnupiravir group vs 14.1% in the placebo group underwent hospitalisation due to COVID-19. Eight patients who received placebo died through day 29, while no deaths were seen in subjects who received molnupiravir.[12] For Paxlovid™, the report of the interim analysis of "EPIC-HR", the phase 2/ 3 trial, showed that among the patients who presented within 3 days of symptom onset, 0.8% of those treated with Paxlovid™ were hospitalised and no deaths were reported whereas, 7% of the patients who received placebo were hospitalised and 7 deaths were reported through 28 days with placebo. Among the subjects who were treated within 5 days of symptom onset, 1% were hospitalised with no deaths reported in Paxlovid™ group, but in the placebo group 6.7% of subjects underwent hospitalisation, and subsequently, 10 among them (1.6%) died.[15]

Both the drugs molnupiravir (acts by inhibiting RdRp) and Paxlovid™ (acts by inhibiting 3CLpro enzyme) prevent SARS-CoV-2 replication and have shown promising results in phase 2/ 3 trials by significantly reducing hospitalisation and death in mild to moderate COVID-19 patients. The antiviral drug, remdesivir, approved for COVID-19 in more than 50 countries including India, the USA, and European Union, has to be given intravenously for 5 to 10 days in patients requiring hospitalisation. Another drug, favipiravir, which is an oral drug, approved in India, Japan, China, and many other countries, has to be given for 7 to 10 days twice daily. The main advantage of molnupiravir and Paxlovid™ is that they can be given orally and the duration of treatment is also short, i.e., 5 days.

Molnupiravir has got approval for marketing in UK and USA and the application is under review with other regulatory agencies like EMA and CDSCO. The drug is likely to get approval from these regulatory bodies soon and will be available in the market in near future. Paxlovid™ has been given EUA by US-FDA and has been approved for marketing in India.

Several drugs have been repurposed and a few new molecules are under trial for COVID-19.[16] As both these drugs (molnupiravir and Paxlovid™) got approval from FDA, there are high chances that they would get marketing authorisation from drug regulatory bodies in other countries as well. It would be potentially useful to lots of patients, especially in the current scenario where most people though they are vaccinated, still have the possibility of getting mild to moderate COVID-19. These drugs will also be useful for people with underlying co-morbidities and having the risk of progression to severe disease. If these drugs are effective in real-world settings, they would be "game changers" in COVID-19 treatment, as we do not have any effective oral anti-viral drugs available currently.

Conclusion

Molnupiravir and Paxlovid™ had significantly reduced hospitalisation and/ or death due to COVID-19 with good safety and tolerability profile. Due to the current pandemic situation, the drugs and vaccines for COVID-19 have been given emergency approval by the regulatory agencies in a short time, based on the positive results observed in the interim analysis of the clinical trials, but we still need more studies in the real world setting in a heterogenous group of population to reaffirm the efficacy and safety of molnupiravir and Paxlovid™.

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